

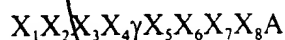
CLAIMS

We claim:

- Sub B1
- 5 1. In a polyamide which specifically binds to base pairs in the minor groove of a DNA molecule, the improvement comprising a positive patch consisting of a rigid group adjacent to a positively charged group such that a positive charge is delivered to the phosphate backbone or the major groove of a DNA molecule.
- 10 2. A polyamide of claim 1 wherein the rigid group comprises a first and a second amino acid; said first amino acid being selected from the group consisting of arginine, proline, lysine, hydroxyproline and a derivative thereof; and said second amino acid being selected from the group consisting of proline, glycine, serine, threonine, leucine, isoleucine, valine, alanine, hydroxyproline and a derivative thereof.
- 15 3. A polyamide of claim 2 wherein said first amino acid is arginine and said second amino acid is proline.
- 20 4. A polyamide of claim 1 wherein the positively charged group comprises a synthetic or naturally occurring amino acid having a net positive charge.
- 25 5. A polyamide of claim 1 wherein said positively charged group is selected from the group consisting of a primary amino group, secondary amino group, tertiary amino group, quaternary amino group, guanidinium group, and an amidinium group.
- Sub B2
- 30 6. A polyamide of claim 1 wherein said positively charged group is selected from the group consisting of arginine, lysine, histidine and a derivative thereof.
7. A polyamide of claim 1 wherein said positively charged group is arginine.

- 25

14. A polyamide of claim 1 having the formula:



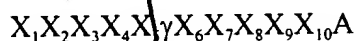
wherein γ is $-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CONH}-$ hairpin linkage derived from γ -aminobutyric acid or a chiral hairpin linkage derived from R-2,4-diaminobutyric acid;

X_1/X_8 , X_2/X_7 , X_3/X_6 , and X_4/X_5 represent four carboxamide binding pairs which bind DNA base pairs and are selected from the group consisting of Hp/Py, Py/Hp, Py/Im, Im/Py, and Py/Py to correspond to the DNA base pair in the minor groove to be bound; and

A represents a positive patch consisting of a rigid group adjacent to a positively charged group such that a positive charge is delivered to the phosphate backbone or major groove of a DNA molecule.

15. A polyamide of claim 14 wherein the positive patch comprises the amino acid sequence Arg-Pro-Arg.

16. A polyamide of claim 1 having the formula:

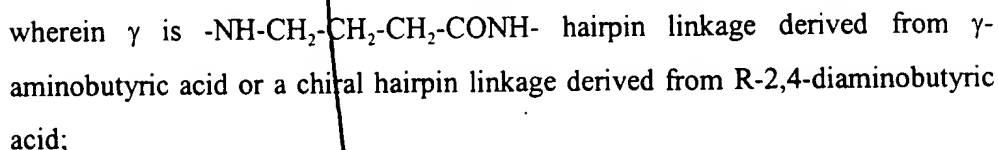


wherein γ is $-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CONH}-$ hairpin linkage derived from γ -aminobutyric acid or a chiral hairpin linkage derived from R-2,4-diaminobutyric acid;

X_1/X_{10} , X_2/X_9 , X_3/X_8 , X_4/X_7 , X_5/X_6 represent five carboxamide binding pairs which bind DNA base pairs and are selected from the group consisting of Hp/Py, Py/Hp, Py/Im, Im/Py, and Py/Py to correspond to the DNA base pair in the minor groove to be bound; and

A represents a positive patch consisting of a rigid group adjacent to a positively charged group such that a positive charge is delivered to the phosphate backbone or major groove of a DNA molecule.

18. A polyamide of claim 1 having the formula:

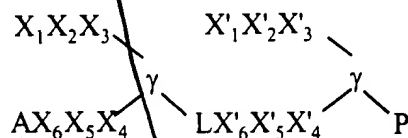


X_1/X_{12} , X_2/X_{11} , X_3/X_{10} , X_4/X_9 , X_5/X_8 , X_6/X_7 represent three or four carboxamide binding pairs which bind DNA base pairs and are selected from the group consisting of Hp/Py, Py/Hp, Py/Im, Im/Py, and Py/Py to correspond to the DNA base pair in the minor groove to be bound; and

A represents a positive patch consisting of a rigid group adjacent to a positively charged group such that a positive charge is delivered to the phosphate backbone or major groove of a DNA molecule.

19. A polyamide of claim 18 wherein the positive patch comprises the amino acid sequence Arg-Pro-Arg.

A tandem-linked polyamide having the formula:



wherein γ is -NH-CH₂-CH₂-CH₂-CONH- hairpin linkage derived from γ -aminobutyric acid or a chiral hairpin linkage derived from R-2,4-diaminobutyric acid;

X_1/X_6 , X_2/X_5 , X_3/X_4 , X'_1/X'_6 , X'_2/X'_5 , X'_3/X'_4 represent carboxamide binding pairs which bind DNA base pairs selected from the group consisting of Hp/Py, Py/Hp,

Py/Im, Im/Py, and Py/Py to correspond to the DNA base pair in the minor groove to be bound;

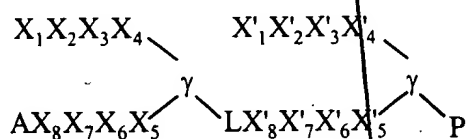
L represents an amino acid linking group selected from the group consisting of β -alanine and 5-aminovaleric acid (δ);

P represents a polyamide selected from the group consisting of

$X_1X_2X_3\gamma X_4X_5X_6$, $X_1X_2X_3X_4\gamma X_5X_6X_7X_8$, $X_1X_2X_3X_4X_5\gamma X_6X_7X_8X_9X_{10}$, and $X_1X_2X_3X_4X_5X_6\gamma X_7X_8X_9X_{10}X_{11}X_{12}$ where X_1 - X_{12} are independently selected from the group consisting of β -alanine, pyrrole, hydroxypyrrole and imidazole; and

A represents a positive patch consisting of a rigid group adjacent to a positively charged group such that a positive charge is delivered to the phosphate backbone or major groove of a DNA molecule.

21. A tandem-linked polyamide having the formula:



wherein γ is $-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CONH}-$ hairpin linkage derived from γ -aminobutyric acid or a chiral hairpin linkage derived from R-2,4-diaminobutyric acid;

X_1/X_8 , X_2/X_7 , X_3/X_6 , X_4/X_5 , X'_1/X'_8 , X'_2/X'_7 , X'_3/X'_6 , and X'_4/X'_5 represent carboxamide binding pairs which bind DNA base pairs selected from the group consisting of Hp/Py, Py/Hp, Py/Im, Im/Py, and Py/Py to correspond to the DNA base pair in the minor groove to be bound;

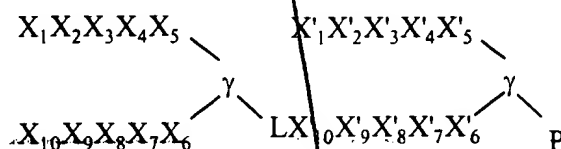
L represents an amino acid linking group selected from the group consisting of β -alanine and 5-aminovaleric acid (δ);

P represents a polyamide selected from the group consisting of

$X_1X_2X_3\gamma X_4X_5X_6$, $X_1X_2X_3X_4\gamma X_5X_6X_7X_8$, $X_1X_2X_3X_4X_5\gamma X_6X_7X_8X_9X_{10}$, and $X_1X_2X_3X_4X_5X_6\gamma X_7X_8X_9X_{10}X_{11}X_{12}$ where X_1 - X_{12} are independently selected from the group consisting of β -alanine, pyrrole, hydroxypyrrole and imidazole; and

A represents a positive patch consisting of a rigid group adjacent to a positively charged group such that a positive charge is delivered to the phosphate backbone or major groove of a DNA molecule.

- 5 22. A tandem-linked polyamide having the formula:



wherein γ is $-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CONH}-$ hairpin linkage derived from γ -aminobutyric acid or a chiral hairpin linkage derived from R-2,4-diaminobutyric acid;

10 X_1/X_{10} , X_2/X_9 , X_3/X_8 , X_4/X_7 , X_5/X_6 , X'_1/X'_{10} , X'_2/X'_9 , X'_3/X'_8 , X'_4/X'_7 , X'_5/X'_6 represent carboxamide binding pairs which bind DNA base pairs selected from the group consisting of Hp/Py, Py/Hp, Py/Im, Im/Py, and Py/Py to correspond to the DNA base pair in the minor groove to be bound;

15 L represents an amino acid linking group selected from the group consisting of β -alanine, 5-aminovaleric acid (δ) and a derivative thereof;

P represents a polyamide selected from the group consisting of

$X_1X_2X_3X_4X_5X_6$, $X_1X_2X_3X_4X_5X_6X_7X_8$, $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$, and $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$ where X_1-X_{12} are independently selected from

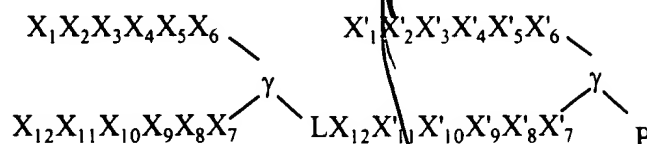
the group consisting of β -alanine, pyrrole, hydrokypyrrole and imidazole; and

20 A represents a positive patch consisting of a rigid group adjacent to a positively charged group such that a positive charge is delivered to the phosphate backbone or major groove of a DNA molecule.

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23. A tandem-linked polyamide of claim 1 having the formula:



wherein γ is $-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CONH}-$ hairpin linkage derived from γ -aminobutyric acid or a chiral hairpin linkage derived from R-2,4-diaminobutyric acid;

X_1/X_{12} , X_2/X_{11} , X_3/X_{10} , X_4/X_9 , X_5/X_8 , X_6/X_7 , X'_1/X'_{12} , X'_2/X'_{11} , X'_3/X'_{10} , X'_4/X'_9 , X'_5/X'_8 and X'_6/X'_7 represent carboxamide binding pairs which bind DNA base pairs selected from the group consisting of Hp/Py, Py/Hp, Py/Im, Im/Py, and Py/Py to correspond to the DNA base pair in the minor groove to be bound;

L represents an amino acid linking group selected from the group consisting of β -alanine, 5-aminovaleric acid (δ) and a derivative thereof;

P represents a polyamide selected from the group consisting of

$X_1X_2X_3X_4X_5X_6$, $X_1X_2X_3X_4X_5X_6X_7X_8$, $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$, and $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$ where X_1 - X_{12} are independently selected from the group consisting of β -alanine, pyrrole, hydroxypyrrole and imidazole; and

A represents a positive patch consisting of a rigid group adjacent to a positively charged group such that a positive charge is delivered to the phosphate backbone or major groove of a DNA molecule.

24. A polyamide of claim 1 selected the group consisting of:

ImPyPyPy- γ -PyPyPyPy- β -RPR;

ImImPyPy- γ -ImPyPyPy- β -RPR;

5 ImPyPyPy- γ -PyPyPyPy- β -RPRRRR;

ImImPyPy- γ -ImPyPyPy- β -RPRRRR;

ImPyPyPy- γ -PyPyPyPy- β -R;

ImPyPyPy- γ -PyPyPyPy- β -RP;

ImPyPyPy- γ -PyPyPyPy- β -RGR;

10 ImPyPyPy- γ -PyPyPyPy- β -R^DPR;

ImPyPyPy- γ -PyPyPyPy- β -APR;

ImPyPyPy- γ -PyPyPyPy- β -KPR;

ImPyPyPy- γ -PyPyPyPy- β -RPK;

ImPyPyPy- γ -PyPyPyPy- β -C7-RPR; and

15 the pharmaceutically acceptable salts thereof.

25. A method of inhibiting gene expression comprising contacting a regulatory sequence of a gene with a polyamide of claim 1.

- 20 26. A method of inhibiting gene expression comprising contacting a DNA molecule with a polyamide of claim 1 whereby the DNA molecule is conformationally constrained.